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Objective: Early postnatal discharge of newborns leads to the risk of readmission to the hospital, mostly for neonatal hyperbilirubinemia. Increasing the length of hospital stay is not an acceptable solution for medical, social and economic constraints. Hence, predicting the high risk neonates for subsequent hyperbilirubinemia is required. This study was planned to investigate the predictive value of umbilical cord blood bilirubin (CBBil) level for significant neonatal hyperbilirubinemia. *Methods*: Cord blood bilirubin, serum total/direct bilirubin levels and newborn/mother's blood groups were obtained from 350 term neonates. Total/direct serum bilirubin levels were reevaluated in 95 newborns at 72 hours of age when jaundice appeared according to Kramer's dermal zones. *Results*: Phototherapy treatment was needed in 14.7% of 95 patients. For recognition the newborns at high risk for developing hyperbilirubinemia, using a CBBil cut-off level of 2.60 mg/dl, we found a positive predictive value of 41.18%, negative predictive value of 97.9% and sensitivity of 50%. *Conclusion*: Newborns with CBBil values below 2.6 mg/dl are at very low risk of developing hyperbilirubinemia and further need of phototherapy. Knowledge of low risk of hyperbilirubinemia in a newborn could encourage the physicians in the decision of early postnatal discharge.

Keywords: Jaundice, hyperbilirubinemia, neonatology

Introduction

The idea of early discharge of maternity patients and newborns was firstly born and practiced in Great Britain in the middle of 20th century [1]. In 1980, Committee on Fetus and Newborn of American Academy of Pediatrics reported the criteria for early infant discharge and follow-up evaluation [2]. The original policy was to discharge the mothers and babies whose condition did not seem to justify further hospital care. Advantages and disadvantages of early postnatal discharge have been discussed in years and readmission to the hospital for neonatal hyperbilirubinemia was noted as one of the remarkable consequences. Re-examining the approach to neonatal jaundice and building up maybe region-based strategies was needed. In the era of "early discharge", in order not to fail to diagnose significant hyperbirubinemia and start the treatment on time, predicting the newborns at high risk of developing hyperbilirubinemia was required. A test to predict hyperbilirubinemia is valuable when it is noninvasive, inexpensive, and available within first day of birth and not required complex equipment especially in developing countries. Umbilical cord blood bilirubin (CBBil), fully covering the criteria, was first published in 1950s by Vest as a marker to predict subsequent severe hyperbilirubinemia [3].

In addition to recent trend, high hospital occupancy rates also gave rise to routine early postnatal discharge practice in Turkey. Similar to many other hospitals in Turkey, in routine daily practice in Zeynep Kamil Maternity and Children's Training and Research Hospital, full-term healthy newborns born via vaginal delivery and cesarean section are staying in hospital, rooming with their mothers for 24 and 48 hours, respectively. Since, postnatal close follow-up might not always be possible for all newborns in our condition, we aimed to verify whether the CBBil level could be used to identify the newborns at high risk of developing subsequent significant hyperbilirubinemia.

Methods

This study was a prospective cohort study, carried out at Zeynep Kamil Maternity and Children's Training and Research Hospital from March 2009 to June 2009.

The study comprised 350 healthy newborns with the following inclusion criteria: gestational age of over 37 weeks according to last menstruation date or by modified Dubowitz's score, ≥2500 g birth weight, ≥7 Apgar scores at the first and fifth minutes of life, normal physical examination. Newborns were free of any known prenatal disease. Mothers and their neonates with any proven hemolytic condition or any complication that could aggravate hyperbilirubinemia in these newborns were excluded. Such conditions included severe bruising, hematoma, sepsis, Down syndrome, hypothyroidism, glucose-6-phosphate dehydrogenase deficiency.

A questionnaire including the information about gender, birth weight, gestation week, type of delivery, oxytocin usage, maternal preeclampsia and premature rupture of membranes, multiple pregnancy, history of a previous sibling with hyperbilirubinemia and Apgar scores at first and fifth minutes was completed for all newborns. Total serum bilirubin level (TSB), direct bilirubin level, blood groups and direct Coomb's test were determined from umbilical cord blood samples of the newborns included in the study. These newborns were followed up during 3-day period and serum total bilirubin levels were detected at 72 hours of age according to evaluation of Kramer dermal zones [4]. The physical examination and the evaluation

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of Kramer dermal zones were performed by the physicians who were unaware of the CBBil levels. Umbilical CBBil and TSB levels were determined via colorimeter method by Roche Cobas Integra 800 autoanalyzer. Direct Coomb's test was detected via microtyping card gel diffusion method by using Diamed-ID centrifuge 12S II device.

A serum bilirubin value ≥17 mg/dl at 72 hours of life was defined as "significant hyperbilirubinemia".

The statistical analysis was carried out using the Statistical Package for the Social Sciences 13.0 (SPSS) program for Windows, *p* values with significance of less than 5% were considered statistically significant. The analysis of the variables under consideration on the basis of the presence of significant hyperbilirubinemia was performed using Student's *t*- or the Mann–Whitney *U*-test for quantitative variables and χ-square for qualitative values. Receiver operator characteristic (ROC) analysis for the prediction of significant hyperbilirubinemia were performed for the CBBil levels with different sensitivity and specificity values.

The study was approved by Zeynep Kamil Maternity and Children's Training and Research Hospital Ethics Committee. Informed consent of the parents was obtained for all the newborns enrolled in the study.

Results

We studied 350 healthy term newborns of a mean gestational age of 39.6 ± 1.3 weeks and a mean birth weight of 3326 ± 499 g. The median value of Apgar scores at 1st and 5th minutes were recorded as 8 and 9, respectively. The documentation of associated risk factors were as follows; oxytocin usage 48.3%, maternal preeclampsia 5.4%, premature rupture of membranes 4.6%, history of a previous jaundiced sibling 2.6% and to be born from a multiple pregnancy 0.9%. The CBBil levels were not different between the newborns with and without risk factors ($p > 0.05$).

Seventy-nine percent of the newborns did not show ABO or Rh blood incompatibility. As expected, there was significant difference in the levels of CBBil between newborns with or without blood incompatibility; the mean CBBil levels were 2.05 ± 0.98 and 1.64 ± 0.41 mg/dl, respectively ($p = 0.001$).

Out of the 350 newborns, 95 (27.1%) developed jaundice and 14 (4%) required phototherapy. Birth weight, gestation week, Apgar scores and gender ratios were not different in jaundiced newborns ($p > 0.05$). CBBil levels of the newborns who received phototherapy were significantly higher than the newborns who did not ($p = 0.001$). Direct Coomb's test positivity was detected in five cases and only one of them received phototherapy. None of the jaundiced babies was required exchange transfusion.

Sensitivity, specificity, positive and negative predictive values, accuracy and relative risk values for each CBBil level were reported in Table I. In analysing the CBBil values to obtain a "cut-off" value to predict subsequent hyperbilirubinemia, ROC analysis was performed (Figure 1). With ROC analysis, a mean CBBil level of 2.6 mg/dl was determined to have the
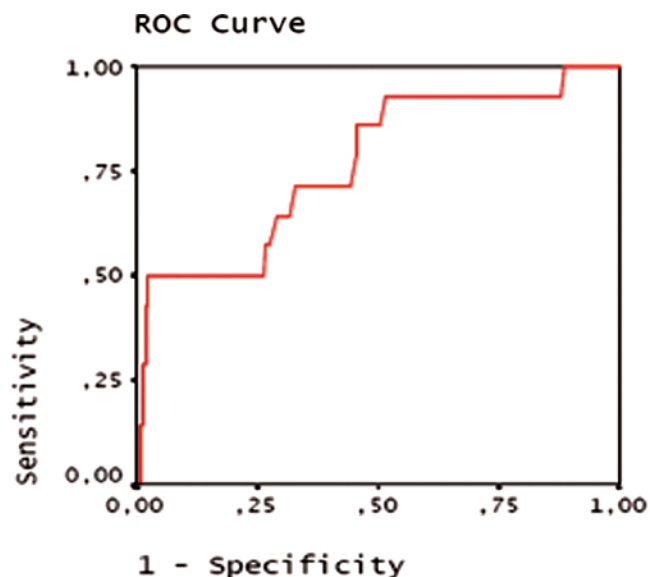

Figure 1. ROC analysis of CBBil levels in predicting subsequent hyperbilirubinemia.

Table I. Sensitivity, specificity, positive and negative predictive values, accuracy and relative risk values for each CBBil level.

Cord blood bilirubin level (mg/l)	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)	Accuracy	Relative risk
1.70	78.57	54.76	6.75	98.40	55.71	4.21
1.74	71.43	57.14	6.49	97.96	57.71	3.18
1.78	71.43	61.61	7.19	98.10	62.00	3.79
1.82	71.43	65.77	8.00	98.22	66.00	4.50
1.86	64.29	68.45	7.83	97.87	68.29	3.68
1.90	64.29	71.13	8.49	97.95	70.86	4.14
1.94	50.00	74.40	7.53	97.28	73.43	2.76
1.98	50.00	77.98	8.64	97.40	76.86	3.32
2.02	50.00	81.55	10.14	97.51	80.29	4.07
2.07	50.00	84.23	11.67	97.59	82.86	4.83
2.10	50.00	86.01	12.96	97.64	84.57	5.48
2.14	50.00	88.10	14.89	97.69	86.57	6.45
2.20	50.00	90.48	17.95	97.75	88.86	7.97
2.25	50.00	92.56	21.88	97.80	90.86	9.94
2.30	50.00	93.15	23.33	97.81	91.43	10.67
2.60	50.00	97.02	41.18	97.90	95.14	19.59
2.70	35.71	97.62	38.46	97.33	95.14	14.40
2.90	50.00	96.13	35.00	97.88	94.29	16.50

highest relative risk (19.59). At the CBBil level of 2.6 mg/dl, the negative predictive value (97.90%) and specificity (97.02%) were fairly high.

The specificity values were getting higher, while the sensitivity values were getting smaller with increasing CBBil levels. Phototherapy was significantly associated with the level of CBBil. Receiving phototherapy was significantly higher in the newborns with ≥2.6 mg/dl CBBil levels ($p = 0.00.$, χ^2: 68.990).

Discussion

Duration of postnatal hospital stay has to be long enough to recognize early neonatal problems and to train the parents about baby care. In the case of high crude birth rate (18.4 births/1000 persons per year in Turkey in 2009) and high hospital occupancy rates, early discharge had become a necessity in Turkey. Problems, associated with early discharge such as hyperbilirubinemia, feeding difficulties and maternal anxiety of having inadequate ability about baby care, had been trying to manage by midwife home visits. In-line with the fact that postnatal follow-up with home visits may not always be possible for all newborns, the main reason for neonatal hospital readmission in our outpatient clinics is neonatal hyperbilirubinemia. In order to minimize both unnecessary hospital stay and bilirubin induced brain damage, identifying the newborns having high risk of subsequent hyperbilirubinemia is needed.

Various screening tests such as measurement of ambient carbon monoxide [5], serum bilirubin on the sixth-hour and first day [6,7], transcutaneous bilirubin (TCB [8,9]) and umbilical cord blood bilirubin [3,10–12] have been used to delineate the newborns susceptible to develop significant hyperbilirubinemia. The measurement of ambient carbon monoxide is entailed highly sophisticated instrumentation and increase in cost. The detection of predischarge serum bilirubin on different hours can be useful but it has the disadvantage of being an invasive method. The TCB bilirubin shows a good correlation with TSB, but may underestimate the serum bilirubin. So, directly applying TCB measurements to TSB nomograms is not recommended [13]. In order to avoid misclassifying the high risk newborns, Rodriguez-Capote et al. recommended to adjust TCB measurements for any observed biases [13].

With the aim of defining a predictor test to be used in also hospitals with limited facilities, we tried to measure the usefulness of CBBil level to predict significant neonatal hyperbilirubinemia. The value of CBBil in Rh and ABO incompatibility was noted in 1950s [14–16]. In 1960, Robinson et al. reported that CBBil levels above 3 mg/dl were highly suggestive of ABO hemolytic disease [17]. Risemberg et al. cited the predictive value of CBBil and suggested that in the case of ABO incompatibility, newborns with cord bilirubin levels greater than 4 mg/dl should be placed in a "high risk" category [10]. On the contrary, in 1978 Haque notified that CBBil was unreliable for predicting hyperbilirubinemia in ABO incompatibility [18].

Umbilical cord blood bilirubin had come up again in eighties and nineties. In a study presented by Whyte and Graham, CBBil was defined as a less reliable indicator and had greater value if used in association with the direct antiglobulin test [19]. In two different studies, Rosenfeld and Knudsen declared that it was possible to define newborns with higher and lower risks of developing significant hyperbilirubinemia by increased CBBil [11,12]. They indicated the levels of 2.0 mg/dl and 2.35 mg/dl (40 µmol/l) or more to have a greater likelihood of developing significant hyperbilirubinemia requiring phototherapy, respectively. For

predicting the need of phototherapy, Knüpfer et al. stated that using a CBBil cut-off level of 30 µmol/l (1.76 mg/dl) revealed a sensitivity of 70.3% and a negative predictive value of 65.6% [3]. CBBil level of 2.2 mg/dl had been reported to show scant sensitivity (22.2%) but high negative predictive value (97.4%) by Carbonell et al. [9]. Considering a cut-off level of 2.0 mg/dl, Bernaldo and Segre concluded that 53% of the newborns with higher CBBil levels would be developed hyperbilirubinemia requiring phototherapy [20]. For recognition of the newborns at high risk for developing hyperbilirubinemia, using a CBBil cut-off level of 2.60 mg/dl, we found a positive predictive value of 41.2%, negative predictive value of 97.9% and sensitivity of 50%. Different CBBil cut-off levels reported by various authors could be explained by the heterogenicity of the study groups. Since a negative predictive value near 100% is important, our data indicate that patients with CBBil values below 2.6 mg/dl are at very low risk of developing hyperbilirubinemia and further need of phototherapy.

Likewise our results, the mean CBBil levels for the newborns who received phototherapy and who did not were also statistically significant in Bernaldo and Segre's series [20].

Since we did not know the number of patients who developed hyperbilirubinemia after the 3rd day, this might be accepted as a limitation for our study and frequency of late onset severe hyperbilirubinemia and its consequences could be a subject for our further large scaled studies.

In conclusion, in case of newborns born in hospital with limited facilities, it is possible to define the group of neonates at risk of developing significant hyperbilirubinemia by using CBBil level. In a newborn defined as having high risk of hyperbilirubinemia, therapeutic intervention might be initiated even earlier than current practice when jaundice appeared. Besides, knowledge of low risk of hyperbilirubinemia in a newborn could encourage the physicians in the decision of early postnatal discharge.

Declaration of Interest: The authors report no conflicts of interest.

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